REMARKS

Reconsideration is respectfully requested.

Claims 1-59 have been canceled. Claims 60-69 are pending and under consideration.

With respect to all amendments and cancelled claims, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional applications.

Rejection Under 35 U.S.C. § 102 (b)

The Examiner has rejected claims 60, 66 and 67 under 35 U.S.C. § 102(b) as alleged anticipated by Meade *et al.* (U.S. Patent No. 6,177,250) (herein after referred to as "*Meade*"). For an anticipation rejection under 35 U.S.C. § 102 to be proper, a single reference must disclose each and every element of a claim. *In re Paulsen*, 31 USPQ2d 1671, 1673 (Fed. Cir. 1994); M.P.E.P. § 2131 (citing *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The Examiner has failed to satisfy the *prima facie* burden on multiple grounds.

A. *Meade* does not teach first and second labeled probes that are both substantially complementary to the same domain.

Claim 60 requires "a first probe" and " a second probe," both of which "substantially complementary to a first domain."

Meade expressly discloses two probes that hybridize to two different domains, not the same domain as required by claim 60. Specifically *Meade* states:

> the first modified single stranded nucleic acid...hybridizes to the first target domain, and the second modified single stranded nucleic acid...binds to the second target domain.
> *Meade* col. 21, lines 59-69.

Further, *Meade* Fig. 2 shows that two single stranded nucleic acids hybridize to different domains of the target sequence. The first target domain and second target domain expressly disclosed by *Meade* are two different domains on the same target sequence. The corresponding first and second probes disclosed by *Meade* hybridize to two different domains of the target sequence instead of the same domain of the target sequence, as required by claim 60. Thus *Meade* does not expressly teach two probes that are both substantially complementary to the same domain.

Meade therefore fails to meet this limitation of claim 60.

B. *Meade* does not expressly teach first and second label probes hybridizing to a the same domain and having different nucleotides at an interrogation position.

Claim 60 requires "a first label probe...comprising a first nucleotide at an interrogation position and...a second label probe...comprising a second nucleotide at said interrogation position." Both the first probe and the second probe are "substantially complementary to the first domain," and have different nucleotides at the "interrogation position."

In addition to not expressly teaching two probes that hybridize to the same domain (as discussed above), *Meade* does not expressly teach that the two probe have first and second nucleotides at the same interrogation position. Rather, *Meade* expressly teaches that the probes hybridize to different domains. *Meade* states:

> the first modified single stranded nucleic acid...hybridizes to a first target domain, and the second modified nucleic acid...binds to the second target domain.
> *Meade* col. 21, lines 59-69.

Further, *Meade* Fig. 2 shows that two single stranded nucleic acids hybridize to different domains of the target sequence. Because the probes hybridize to different locations, they do not have different nucleotides at the same interrogation position.

In sum, different domains on the target nucleotide are at different locations, and cannot hybridize to the same position. The two probes disclosed by *Meade* thus do not have an interrogation position in common, and so cannot have first and second nucleotides in common at an interrogation position. *Meade* therefore does expressly not teach an interrogation position as claimed.

Because Meade fails to expressly teach multiple limitations of claim 60 and those depending therefrom, the rejected claims are not anticipated by *Meade*. This ground for rejection should be withdrawn.

Rejection Under 35 U.S.C. § 102(e)

The Examiner has rejected claim 60, 64 and 66-69 under 35 U.S.C. § 102(e) as alleged anticipated by Blackburn *et al.* (U.S. Patent No. 6,686,150) (herein after referred to as "*Blackburn*").

A. *Blackburn* does not expressly teach first and second labeled probes that hybridize to the same first target domain.

Claim 60 recites "a first label probe...comprising a first nucleotide at an interrogation position and...a second label probe...comprising a second nucleotide at said interrogation position."

Blackburn expressly discloses two probes that hybridize to two different domains, not the same domain as required by claim 60. The Examiner points to Fig. 16H and col. 7, lines 44-46 for support for this rejection. However, Fig. 16H shows different probes hybridized to different locations on the target nucleotide. Specifically, probe 145 hybridizes to one domain of target 120, and probe 110 hybridizes to a second domain of target 120. The probes hybridize to different domains, not the same "first domain" of

claim 60. Because *Blackburn* expressly discloses probes hybridize to different domains of the target and not the same "first domain" of the target as required by claim 60, the reference fails to teach every limitation of claim 60.

Therefore, *Blackburn* does not expressly meet this limitation of claim 60.

B. *Blackburn* does not expressly teach first and second probes having different nucleotides at the same interrogation position.

Claim 60 recites "a first label probe...comprising a first nucleotide at an interrogation position and...a second label probe...comprising a second nucleotide at said interrogation position." Both the first probe and the second probe are "substantially complementary to the first domain," and have different nucleotides at the "interrogation position."

Claims 60 not only requires that two probes do not hybridize to the same domain, as discussed above, but also requires that the two probes have different nucleotides at the same interrogation position. *Blackburn*, however, expressly teaches that the probes hybridize to different domains. In Fig. 16H, the probes do not hybridize to the same target domain, and thus cannot have first and second nucleotides, respectively, at the same interrogation position. Therefore, *Blackburn* does not expressly teach this limitation of claim 60.

For purpose of anticipating claim 60, *Blackburn* fails to disclose each and every element of the claim 60. Therefore, claim 60 and claims 64 and 66-69 dependent thereon are not anticipated by *Blackburn*. Applicants respectively request that this ground for rejection be withdrawn.

Rejection Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 61-65 under 35 U.S.C. § 103(a) as allegedly unpatentable over *Meade* in view of Heller *et al.* (U.S. Patent No. 5,605,662) (herein after referred to as "*Heller*"). The Examiner also rejected claims 66-69 under 35 U.S.C.

§ 103(a) as allegedly unpatentable over *Meade* in view of Kayyem *et al.* (U.S. Patent No. 6,096,273) (herein after referred to as "*Kayyem*").

To establish a *prima facie* case, three basic criteria must be met: (1) the prior art reference(s) must teach or suggest each and every limitation of the rejected claims; (2) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine their teachings; and (3) there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not in Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. §2142.

A. Claims 61-65 are not obvious over *Meade* in view of *Heller*.

1. Claims 61, 62, 64 And 65 do not include "an array."

The Examiner has rejected claims 61-65 under 35 U.S.C. § 103(a) as being allegedly unpatentable over *Meade* in view of *Heller*, on the basis that "Heller et al. teach an array." Applicant submits that only claims 63 includes "an array."

Accordingly, Applicant requests the withdrawal of rejection of claims 61, 62, 64 and 65 under 35 U.S.C. § 103(a) as allegedly unpatentable over *Meade* in view of *Heller*.

2. *Meade* And *Heller*, in combination, do not expressly disclose every limitation of the claimed methods.

As set forth in the section above discussing anticipation, *Meade* fails to expressly teach the method of determining the identification of nucleotide(s) set forth by claim 60. Applicants emphasize that *Meade* does not expressly teach: (1) first and second label probes, both substantially complementary to the first domain; and (2) each first and second label probes having different nucleotides at the same interrogation position. *Heller* does augment the teaching of *Meade*. Thus, *Meade* and *Heller* taken together do not teach all of the elements of independent claim 60, and of claims 61-65 dependent thereon.

Because neither *Meade* nor *Heller* expressly teach every limitation of the claimed invention, the claims are not obvious.

3. There is no motivation to combine the references because *Heller* combining *Meade* with the teachings of *Heller* would result in an inoperable device.

A proposed modification cannot render the alleged prior art unsatisfactory for its intended purpose. *See* M.P.E.P. § 2143.01.

Meade discloses methods of determining the presence of a sequence by hybridizing two separate nucleic acids to different domains of a target nucleotide. Conduction occurs when hybridization occurs, and conduction does not occur in the absence of hybridization.

Detecting a change in an electrical signal would not be possible using the devices of *Heller*. This is because *Heller* teaches a device in which an electrical connection is maintained between the ETM and electrode via a conductive solvent and changes in electrical signals would not be detected.

Heller teaches a permeation layer that could only physically separate the electrode and the ETMs. Heller states:

> an array of electronically self-addressable microscopic locations. Each microscopic location contains an underlying working direct current (DC) micro-electrode supported by a substrate. The surface of each micro-location has a permeation layer for the free transport of small counter-ions, and an attachment layer for the covalent coupling of specific binding entities.
> *Heller* col. 6, lines 44-50.

Thus, the permeation layer described by *Heller* allows free transport of counter ions that would not electrically separate the electrode and ETMs, and would thereby result in a constant electrical connection between the electrode and the ETMs. Specifically, *Heller* teaches that "[t]he permeation layer provides spacing between the metal surface and the attachment/binding entity layers and allows solvent molecules, small counter-ions, and gases to freely pass to and from the metal surface." *See* Figure 2; col. 10, line 65 to col.

11, line 2. *Heller* further teaches that "[a] functional device requires some fraction (-5% to 25%) of the actual metal micro-electrode surface to remain accessible to solvent (H_20) molecules, and to allow the diffusion of counter-ions (e.g., Na^+ and Cl^-) and electrolysis gases (e.g., O_2 and H_2) to occur." *See* col. 13, lines 41-46. Thus, although the permeation layer as taught by *Heller* can keep reactants physically separated, it does not keep them electrically separated.

A permeation layer such as *Heller*'s that is not electrically separated allows constant electrical conduction between components such as ETMs and electrodes. This constant conduction results in permanent signal being detected on the electrode. *Meade*, however, describes a system in which electrical conduction is not constant, but rather only occurs between the ETM and electrode when hybridization occurs. *Heller*, when combined with the disclosure of *Meade*, would cause constant conduction whether or not a probe was hybridized to the target. The combination of *Heller* with *Meade* would thus result in an inoperable device, since no difference in electrical signal could be detected when a probe is hybridized versus unhybridized.

4. There is no reasonable expectation of success for combining the cited references, because the combined device would be inoperable.

As discussed above, *Heller* discloses a device in which a permeation layer is permeated with conductive solvent. The conductive solvent provides a constant electrical connection between the electrode and an ETM. Thus, even though there may be a physical separation between the electrode and ETMs, the electrical connection remains intact. Specifically, *Heller*'s permeation layer requires some fraction (-5% to 25%) of the actual metal micro-electrode surface to remain accessible to solvent (H_20) molecules, and to allow the diffusion of counter-ions through the permeation layer. Because the metal surface of the electrode is in contact with the solvent (water), and there is diffusion of counter-ions, there is constant conduction through the electrode. This constant conduction would result in constant signal being detected on the electrode regardless of whether the probe is hybridized to the target nucleic acid. Because a constant signal

irrespective the presence or absence of target sequences would result from the combination of *Meade* with *Heller*, one would not have a reasonable expectation of combining the references.

Because the combined references (1) fail to teach every claimed limitation, (2) would not be physically operable and teach away from the claimed invention, and (3) would not provide one of skill in the art with a reasonable expectation of success in making the claimed invention, claims 61-65 are not obvious over *Meade* in view of *Heller*.

Applicants respectfully request that this ground for rejection be withdrawn.

B. Claims 66-69 Are Not Obvious Over *Meade* In View Of *Kayyem*

Claims 66-69 stand rejected under 35 U.S.C. § 103(a) over *Meade* in view of *Kayyem*. Under 35 U.S.C. § 103(c)(1), *Kayyem* cannot preclude patentability of the presently claimed invention under U.S.C. § 103.

35 U.S.C. § 103(c)(1) states:

> [s]ubject matter developed by another person, which qualifies as prior art only under one or more of subsections (e), (f), and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Kayyem cannot be used in an obvious rejection under 35 U.S.C. § 103(a) if the reference could only qualify as prior art under 35 U.S.C. § 102(e), (f), or (g), and was owned by the same entity or subject to an obligation of assignment to the same entity as the instant application at the time the claimed invention was made.

1. Because *Kayyem* is not a prior art reference under 35 U.S.C. §§ 102(a), (b), (c), or (d), *Kayyem* could only be an alleged prior art reference under 35 U.S.C. §§ 102(e), (f), or (g).

Kayyem is not prior art under 35 U.S.C. §§ 102(a), 102 (b), 102(c) or 102(d). Therefore, *Kayyem* could only be considered as alleged prior art under 35 U.S.C. §§ 102(e), (f), or (g).

2. Statement of Common Ownership

In accordance with the requirements to establish common ownership articulated in M.P.E.P. § 706.02(l)(2), the instant U.S. Patent Application No. 09/626,096 and the *Kayyem* patent were, at the time the invention of the instant application was made, owned by Clinical Microsensors, Inc.

Therefore, according to U.S.C. § 103(c)(1), *Kayyem* cannot preclude patentability of the presently claimed invention under U.S.C. § 103. Because this ground for rejection is improper, Applicants respectfully request that it be withdrawn.

CONCLUSION

Applicants respectfully submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. If the Examiner feels there are further unresolved issues, the Examiner is respectfully requested to phone the undersigned at (415) 781-1989.

RESPECTFULLY SUBMITTED,

DORSEY & WHITNEY LLP

DATE NOVEMBER 14, 2005 **BY** _____

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